

References

1. Milanowski J, Qualtrough J, Perrin V. Inhaled beclomethasone (BDP) with non-CFC propellant (HFA 134a) is equivalent to BDP-CFC for the treatment of asthma. *Respir Med* 1999; **93**: 245–251;
2. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokin Biopharm* 1987; **15**: 657–680.

Dear Sir

Response to letter of Dr Zanen re: paper by Milanowski *et al.* (*Respir Med* 1999; 93: 245–251)

We thank Dr Zanen for his reasoned statistical comments on the studies (1,2). However, the aim of the two studies was to demonstrate therapeutic equivalence between the BDP-CFC and BDP-HFA inhalers based on meaningful clinical differences in everyday practice. Unfortunately, Dr Zanen's assumption that equivalence was based on a lack of statistically significant differences between the two preparations is incorrect given that the conclusions of equivalence were derived from comparisons of confidence intervals for the between-treatment difference and an acceptable range considered to be clinically equivalent.

The significant and equivalent improvements in lung function and asthma symptoms seen with both BDP-CFC and BDP-HFA in these studies are entirely consistent with the literature on similar inhaled steroid studies. Minor numerical differences in lung function indices and standard deviations between populations are unlikely to matter in clinical practice, as has been borne out by successful transfer of asthma patients from the BPD-CFC to the BDP-HFA inhaler on a 1:1 dose basis since introduction of the latter product to the market in Ireland 18 months ago.

We reiterate our belief that the sample sizes chosen in these studies were based on clinically relevant differences and that the products are indeed equivalent in both meaningful statistical terms and in clinical practice.

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References

1. Milanowski J, Qualtrough J, Perrin V. Inhaled beclomethasone (BDP) with non-CFC propellant (HFA 134a) is equivalent to BDP-CFC for the treatment of asthma. *Respir Med* 1999; **93**: 245–251.
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Dear Editor

Inhaled beclomethasone (BDP) with non-CFC propellant (HFA-134a) is equivalent to BDP-CFC for the treatment of asthma: Milanowski *et al.* (*Respir Med* 1999; 93: 245–251)

I read with interest the paper from Milanowski *et al.* on the equivalence of BDP-HFA to BDP-CFC. This is based on two studies, one low dose (400 mcg day⁻¹ BDP) and one high dose (2000 mcg day⁻¹). The results of these studies I think should be viewed with caution but open up some interesting areas of debate.

The statistical analysis for both studies was based on testing for difference. This was defined as a difference in mean pre-dose FEV₁ of >0.2 l. The results clearly show that the 90% confidence interval for the high dose study (–0.34–0.5) lies outside ±0.2 l. Similarly for the low dose study the 90% confidence interval is (–0.14–0.35), again lying outside the upper end of the pre-defined ±0.2 l.

It is stated that the total number of patients needed to detect a statistical difference with 90% power using 90% confidence intervals was 100. The standard deviation for FEV₁ in both studies was around 0.8 l. To detect equivalence or difference, based on these assumptions, the total number of patients needed would be 275 and 338 per treatment group respectively, greatly in excess of 100. It would therefore appear that these studies are both under-powered and inconclusive. Consequently the interpretation by Milanowski *et al.* that BDP-CFC and BDP-HFA (Norton Healthcare Ltd, U.K.) are clinically and statistically equivalent should be viewed with caution.

The dosing schedule of qds dosing is not in line with the British Asthma Guidelines and would have led to poor compliance in some subjects. The rationale behind this schedule needs to be justified. In the high dose study a very wide-ranging group of patients (taking 800–2000 mcg day BDP⁻¹) were randomized to 2000 mcg of either BDP-HFA or BDP-CFC patients. This wide variability may account for the large confidence intervals seen in this study, but underlies the need to conduct robustly designed efficacy and safety studies as well as dose response studies.

The study also considers safety, as measured by adverse events and am plasma cortisol. Morning plasma cortisol is a very variable measure and studies using 24 h urinary free cortisol would be a more helpful measure to define any clinically relevant difference between the two formulations.

Conflict of interest: JGA is a medical advisor to Merck, Sharpe & Dohme, Schering Plough and AstraZeneca. He was chairman of the steering group that oversaw the SAMM study for 3M's product Airomir and currently fulfil the same role for the QVAR SAMM study.